REMARKS

Claims 1-21 are pending and stand rejected. Claim 1 has been amended to clarify that the fluorescence anisotropy of the fluorophore is measured when the fluorophore-labeled aptamer is bound to the analyte and that the presence or amount of analyte is identified when the measured fluorescence anisotropy is greater than an anisotropy measurement obtained in the absence of bound analyte. Support for this amendment can be found throughout the claims and the specification, for example, in paragraphs 0089-0096 of the submitted specification. No new matter has been added by this amendment. Applicants are pleased to note that Claims 2-7 would be allowable if the rejection under 35 U.S.C. §112 is overcome and these claims are rewritten to include the elements of the independent claim.

35 U.S.C. §112, Second Paragraph, Definiteness

Applicants note that the Examiner's reading and understanding of the claim is correctly stated on page 2 of the Office Action. That is, the aptamers do bind to the analyte. Applicants have accordingly added the element of "said fluorophore-labeled aptamer is bound to said analyte" to Claim 1 to more explicitly describe how analyte detection occurs. In view of this amendment, Applicants request that the rejection be withdrawn.

The Claims are non-obvious over Gold in view of Tomei

Claims 1, 9, 11, 12, 14, 15, and 17-21 stand rejected under 35 U.S.C. §103 as being unpatentable over Gold et al. (U.S. Pat. No. 6,544,776, "Gold") in view of Tomei et al. (U.S. Pat. No. 5,037,207, "Tomei"). The Examiner has asserted that Tomei teaches a means of direct polarized illumination for fluorescence anisotropy and noted that the advantage of Tomei's system is that it eliminates the need for mechanical translation of a stage. The Examiner also found that the device in Tomei is capable of scanning targets of any size without gross stage movement and concluded that one of skill in the art, at the time of the invention, would have combined the teaching of Gold (regarding aptamers on biochips, discussed in the previous Responses) with the method of Tomei, in order to obtain a method in which direct observation of changes in anisotropy of a fluorophore could be achieved. Applicants respectfully traverse the rejection.

Applicants note that while Tomei does disclose anisotropy as a means of monitoring a sample for the presence of fluorescent *cells*, the skilled artisan would not have been motivated to combine measurement of anisotropy performed by Tomei with the measurements of the changes in anisotropy in Gold, which involve fluorophores attached to *individual aptamers* that are attached to a surface, not whole cells. Moreover, given the knowledge in the art, the skilled artisan would not have expected the method of Tomei to be applicable to the system in Gold and would not have expected the proposed combination of Tomei and Gold to work. As there would have been no motivation for the combination and no expectation of success, a *prima facie* case of obviousness has not been established. (M.P.E.P. § 2143.02).

As noted in the previous Responses, the claimed method involves the measurement of changes in anisotropy of a fluorophore that is attached to an aptamer. Importantly, the aptamer is attached to a solid substrate throughout the method. As established by 1) the previous art of record, 2) the previously submitted Responses, and 3) the art currently cited by the Examiner (especially Potyrailo, which was also cited previously), at the time of the filing of the application, one of skill in the art would have operated under the assumption that changes in anisotropy depend upon large changes in the mobility of the fluorophore. Changes in mobility were linked to the mass or size of the object. For example, changes in anisotropy would have been expected when a fluorophore goes from freely moving in solution to being bound to a substrate. Put another way, changes in anisotropy would occur when the fluorophore goes from being "small" (or a freely rotating molecule) to being part of a large (or relatively immobilized) complex.

Additionally, as established in the previous Responses and art of record, it was believed that fluorophores that are already attached to a substrate would have very small changes (or no changes) in anisotropy upon the binding of an additional compound. This was assumed to be the case because the fluorophore was already attached to a relatively large substrate, and thus, already had a huge mass. Because of this, the addition of a smaller mass would have been expected to have little or no impact on the anisotropy of the fluorophore.

In light of these beliefs, the art (*e.g.*, Potyrailo) taught that particular, specific techniques were to be used for measuring changes in anisotropy in which a fluorophore was already associated with a substrate (that is, when the fluorophore had a large mass). In order to be able to detect the expected small change in anisotropy, these techniques emphasized noise reduction and signal sensitivity as important for the methods. At the time of the invention, one of skill in the

art would have believed that changes in anisotropy due to the binding of an analyte to an aptamer that was already attached to a substrate would not have been detectable through a direct illumination technique.

Tomei does not rebut the previous teachings and, importantly, does not teach or suggest that their disclosed techniques would be applicable to, or would be likely to work for systems in which fluorophores are associated with a solid support via aptamers. Thus, Tomei is insufficient to establish a *prima facie* case of obviousness.

Tomei teaches a device that is useful in scanning a large area of a microscope slide for imaging the location and presence of whole cells. Tomei does not teach or suggest that their particular device or techniques should be used, or could be used, to detect changes in anisotropy that are on the scale of fluorophores attached to aptamers, which in turn are attached to a solid support. To the contrary, Tomei's use for anisotropy is to image entire cells (see Fig. 3), which involves detection limits and requirements that are very different from those described to be important in Potyrailo and Gold for measuring changes in anisotropy of fluorophores attached to individual aptamers at the molecular level. As a result, Tomei's system would require significant modification to be used in the cited combination.

One of skill in the art would not have been motivated to combine the technique disclosed in Tomei with Gold and make the necessary modifications without something that would suggest that it could be successfully used in the system of Gold. Tomei has no teaching or suggestion that the device could (or should) be used where the change in the signal is on the scale of molecules instead of cells and where changes in the relative mass of the fluorophore are as small as they would have been expected to be in the methods described in Potyrailo or Gold.

Applicants note that Tomei states that "[t]he system is capable of scanning targets of any size without gross stage movement...." However, this statement cannot be taken in isolation. Read in the context of the entire patent, the statement does not suggest that the device in Tomei allows for the detection of targets of any size, but rather that gross stage movement is not required when Tomei's device is used in a disclosed system (see FIG. 3 depicting the scanning ability of the device). Tomei has no teaching or suggestion that a detectable signal could be obtained by direct illumination of a fluorophore-labeled aptamer bound to a solid support. Thus, there is no suggestion of combining Tomei's device and/or methods with the system disclosed by Gold to arrive at the present invention or that such a combination would work.

Finally, Applicants note that the prior art generally taught away from the use of direct illumination and observation of the anisotropy of a fluorophore that is continuously associated with an aptamer, which is attached to a solid support. As demonstrated in Potyrailo, the art considered the detection of changes in anisotropy, for these particular applications, to be very small. Indeed, Potyrailo, which claims to teach the "first aptamer-based biosensor that can be used to detect free and nonlabeled non-nucleic acid targets" (p. 3419), explicitly notes that "an important advantage of using an evanescent wave over direct sample illumination is a greatly reduced illuminated volume and a similarly reduced background." (p3422, emphasis added). Applicants note that all of the teachings in Potyrailo involve the use of an evanescent field (indirect illumination). Thus, the state of the art (involving substrate associated fluorophores), at the time of filing, actually taught away from the cited combination.

In view of the lack of motivation in the references themselves or the art as a whole for the combination of Tomei and Gold, the lack of any expectation of success in the combination and the actual teaching away in the art, Applicants submit that a *prima facie* case of obviousness has not been established and request that the rejection be withdrawn.

The Claims are non-obvious over Potyrailo in view of Tomei

Claims 1, 8, 9, 11-13, and 16 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Potyrailo et al. in view of Tomei. Applicants note that the arguments presented above apply to this rejection as well and that the particular references do not overcome the above identified deficiencies. As such, one of skill in the art would not have been motivated to combine the teachings of Potyrailo and Tomei to arrive at the claimed invention and would not have expected the asserted combination to be successful. Additionally, the art, including Potyrailo itself, actually taught away from the combination. Thus, Applicants request that this rejection be withdrawn as well.

Claim 10 is non-obvious in view of the above combined with Wei.

Claim 10 was rejected under 35 U.S.C. § 103(a) as being unpatentable over Potyrailo et al. in view of Tomei and Wei (U.S. 6,576,419). Claim 10 depends from Claim 1 and contains all of the features thereof, in addition to further distinguishing features. Wei was found to teach particular fluorophores but does not overcome the above identified deficiencies in the

combination of Potyrailo and Tomei. Thus, in view of the patentability of Claim 1, as discussed above, Applicants request that this rejection be withdrawn.

Conclusion

Applicants respectfully submit that for the above-recited reasons the rejections should be withdrawn and the claims allowed. If, however, some issue remains, the Examiner is cordially invited to telephone the undersigned in order to resolve such issue promptly. Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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